STUDY OF RISK FACTORS IN ISOLATED HYPOSPADIA PATIENTS

RESEARCH ARTICLE

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ABSTRACT

Background : *The incidence of hypospadia tends to increase while the etiology is still unclear. The risk factors of hypospadia have not been studied yet in Indonesia. The purpose of this research is to count the proportion of some suggested risk factors of isolated hypospadia particularly patients who referred to Center for Biomedical Research (CEBIOR) laboratory.*

Method : *This research design was descriptive study with cross sectional approach involving 95 parents of isolated hypospadia patients ranging from 0-24 years old as the sample. The data was collected by means of AGORA questionnaire. The data were tabulated and processed using Microsoft excel to be presented in table and diagram.*

Result : *Proportion of paternal risk factor : 50% from 95 respondents were actively smoke, 17% were exposed to pesticide, 2% were subfertile father, 1% has cryptorchidism history. The proportion of maternal risk factors : 25% from 95 respondents had low birth weight baby, 12% had pregnant in advance age, 9% were exposed to pesticide, 9% were using contraception, and 3% had twin baby.*

Conclusion : *The proportion of paternal risk factor with descending fashion respectively are active smoking, pesticide exposure, subfertile status, cryptorchidism history, and hypospadia history, while in mother are low birth weight, advance age of pregnancy, maternal contraception, pesticide exposure, and twin pregnancy. Some respondents who have more than 1 risk factor might explain that hypospadia occurs as multifactorial disease.*

Keyword : *isolated hypospadia, risk factor, proportion.*

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Studi Faktor Resiko pada Pasien Isolated Hypospadia

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ABSTRAK

Latar belakang : Insiden hypospadia semakin tahun cenderung meningkat, namun hingga sekarang etiologinya masih belum jelas. Di Indonesia, belum ada penelitian mengenai faktor resiko hypospadia. Penelitian ini bertujuan menghitung proporsi beberapa faktor resiko yang diusulkan berperan pada kejadian hypospadia ringan (Isolated Hypospadia) khususnya yang dirujuk ke laboratorim *Center for Biomedical Research (CEBIOR)*

Metode : Desain penelitian ini adalah deskriptif dengan pendekatan *cross sectional*, dengan 95 sampel orang tua dari pasien isolated hypospadia yang berusia sekitar 0 - 24 tahun yang telah berhasil diambil datanya menggunakan questionnaire dari AGORA. Data yang terkumpul ditabulasi dan diolah dengan *Microsoft Excel* untuk ditampilkan dalam tabel dan diagram.

Hasil : Proporsi faktor resiko ayah : 50% dari 95 responden aktif merokok pada periode tertentu, 17% terpapar pestisida pada periode tertentu, 2% berstatus subfertil, 1% memiliki riwayat cryptorchidism. Proporsi faktor resiko ibu : 25% dari 95 responden melahirkan bayi BBLR, 12% hamil diusia tua, 9% terpapar pestisida, 9% menggunakan kontrasepsi, dan 3% responden memiliki bayi kembar.

Simpulan : Proporsi faktor resiko dari tinggi ke rendah pada ayah berturut-turut adalah merokok aktif, paparan pestisida, status subfertil, riwayat cryptorchidism, riwayat hypospadia. Sedangkan pada ibu adalah BBLR, usia hamil tua, penggunaan kontrasepsi, paparan pestisida, dan kehamilan kembar. Terdapatnya responden yang memiliki lebih dari 1 faktor resiko mungkin menjelaskan bahwa hypospadia terjadi karena interaksi banyak faktor.

Kata kunci : isolated hypospadia, faktor resiko, proporsi

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BACKGROUND

Hypospadia is the most congenital malformation of penile urethra, characterized by incomplete fusion of urethral folds with abnormal opening of urethra and different degree of penile curvature.[1] Hypospadia affects approximately 1 in 250 newborn or roughly 1 in 125 live male birth in United Stated.[2,3] It can occur as isolated or non isolated defect.

The incidence of this disease tends to increase including the incidence in Asian.[4,5,6] Between June 2000 - December 2009, about 156 cases were referred to CEBIOR (Centre for Biomedical Research), Faculty of Medicine Diponegoro University by Urology Department Faculty of Medicine Diponegoro University – dr. Kariadi Hospital where all the patients come from Semarang and surrounding area.

Moreover, even though hypospadia is commonly occur and the studies about genetics, endocrine, and environmental impairment have been proposed, the etiology of hypospadia remain unclear and elusive.[7,8,9] Hypospadia appears to be multifactorial in which each factor may correlate each other.[2]

Almost all studies about risk factors suggested were conducted in Europe and mostly in Caucasian race. There is no report of such study conducted in Indonesia yet. By this study, the researcher wants to know the proportion of some risk factors suggested which are paternal subfertile status, father with hypospadia history, father with cryptorchidism history, paternal active smoking, paternal pesticide exposure, maternal pesticide exposure, maternal contraceptive, advance age of pregnancy, low birth weight infant, and twin or triplet pregnancy as risk factors of hypospadia.

METHODS

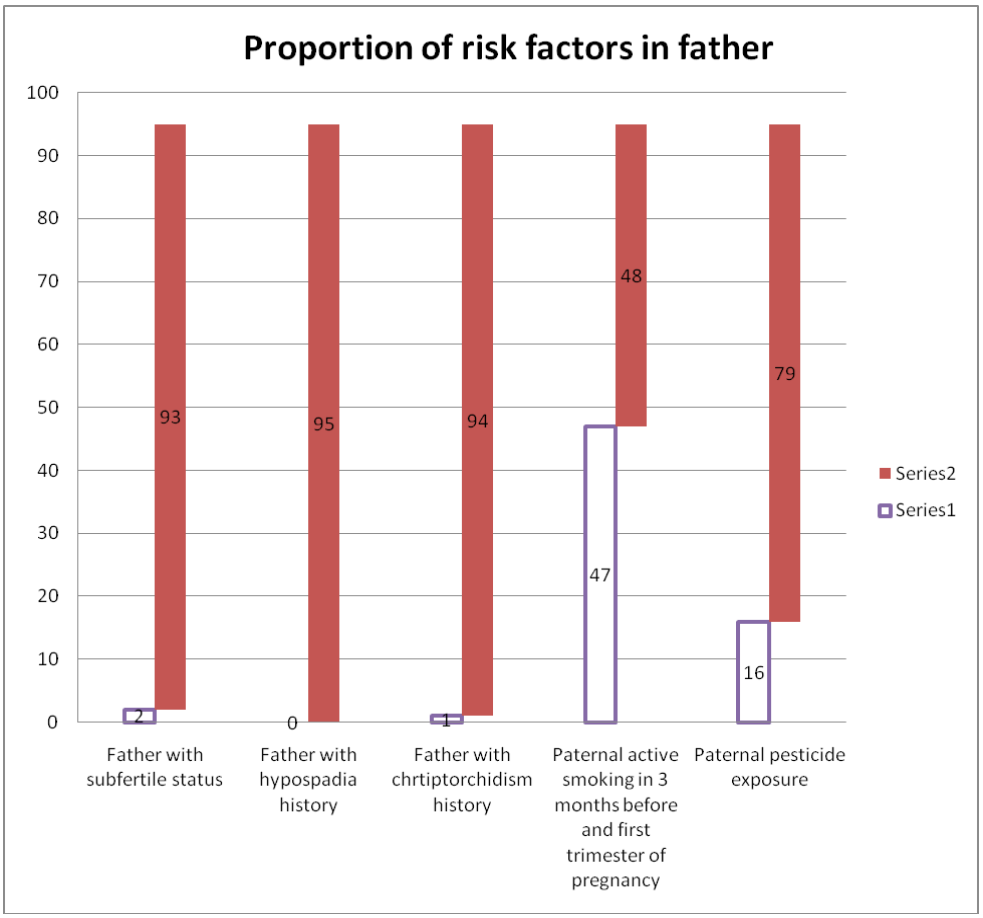
Sample gathered in this study was 95 pairs of parent of isolated hypospadia patient who referred to Center for Biomedical Research (CEBIOR) during 2000 until May 2010 with the range of age of patient was 0 to 24 years old. The data was collected by means of questionnaire. Some of questionnaires had already been taken as part of AGORA (Aetiological Research into genetic and occupational/environmental risk factors for anomalies in children) conducted by Center for Biomedical Research (CEBIOR) and Radboud University Nijmegen Medical Center and some incomplete data were traced back by phoning the respondents. Samples included in this study were parents of patients who are diagnosed as isolated hypospadia, agree to join this research, and complete the whole questionnaire.

RESULT

Samples gathered are parents of isolated hypospadia patients. The range of age of patients is 1 month to 22 years old. The average age of patients until the day of interview is 8 years old. The youngest age of father is 25 years old, and the oldest is 60 years old. The range of age of mother is 22 to 58 years old on the day of interview.

The comparative portion of each risk factor between 95 father respondents is shown in diagram 1.1.

Diagram 1.1 :

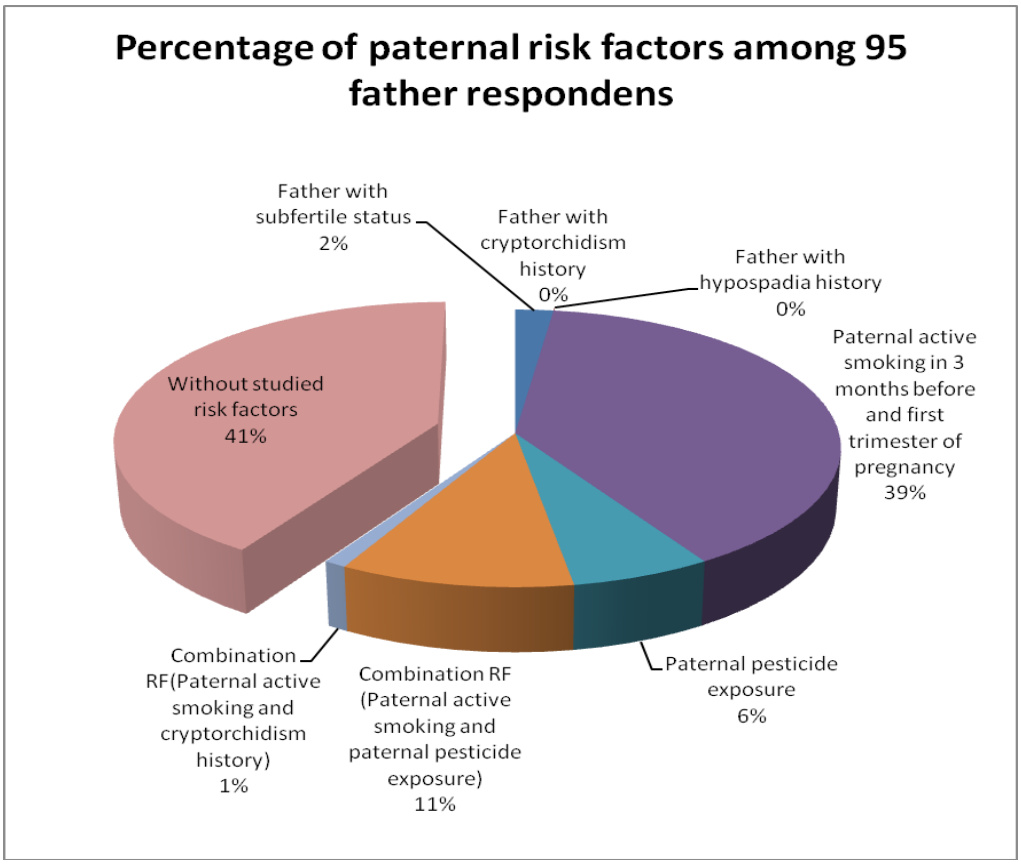


Series 1 : respondent with risk factor

Series 2 : respondent without risk factor

The percentage of paternal risk factors including its combination (more than 1 risk factor) is shown in pie diagram 1.2.

Diagram 1.2 :

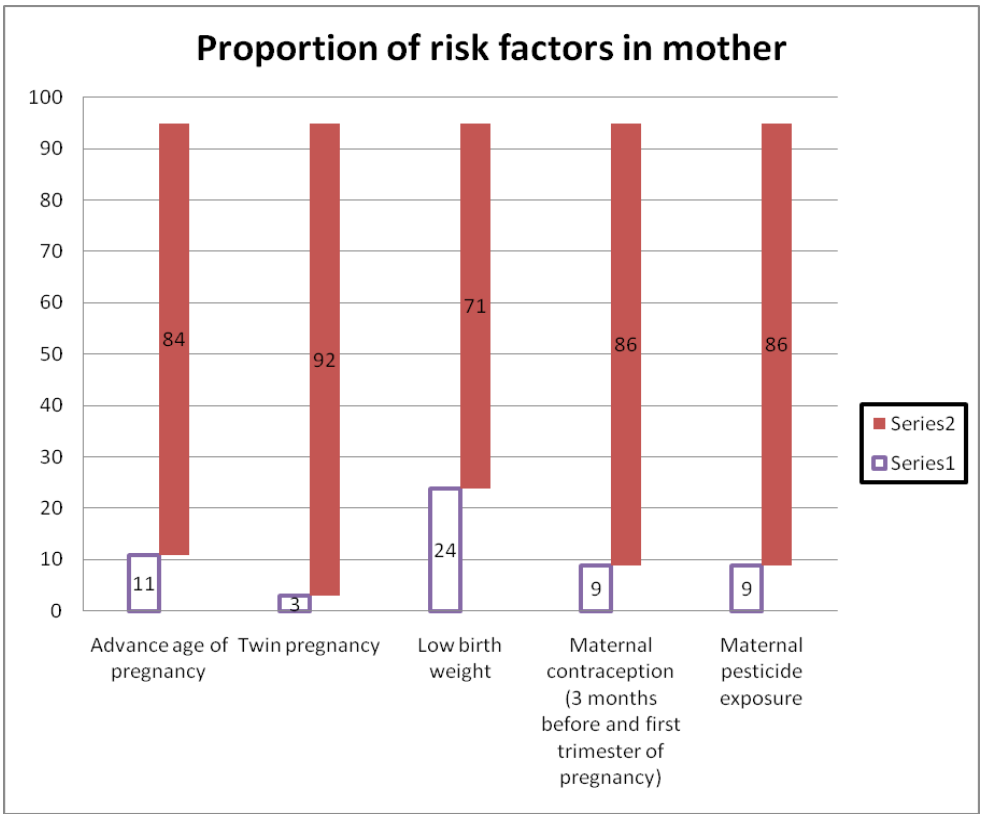


RF : risk factor

The highest proportion of paternal risk factors among 95 respondents is paternal active smoking (39%), followed by 11% of combination RF (paternal active smoking-pesticide exposure), pesticide exposure (6%), subfertile status (2%), 1% with combination RF (paternal active smoking-cryptorchidism history. Forty one percent is other risk factors that were not studied.

The comparative portion of each risk factor between 95 mother respondents are shown in diagram 2.1

Diagram 2.1

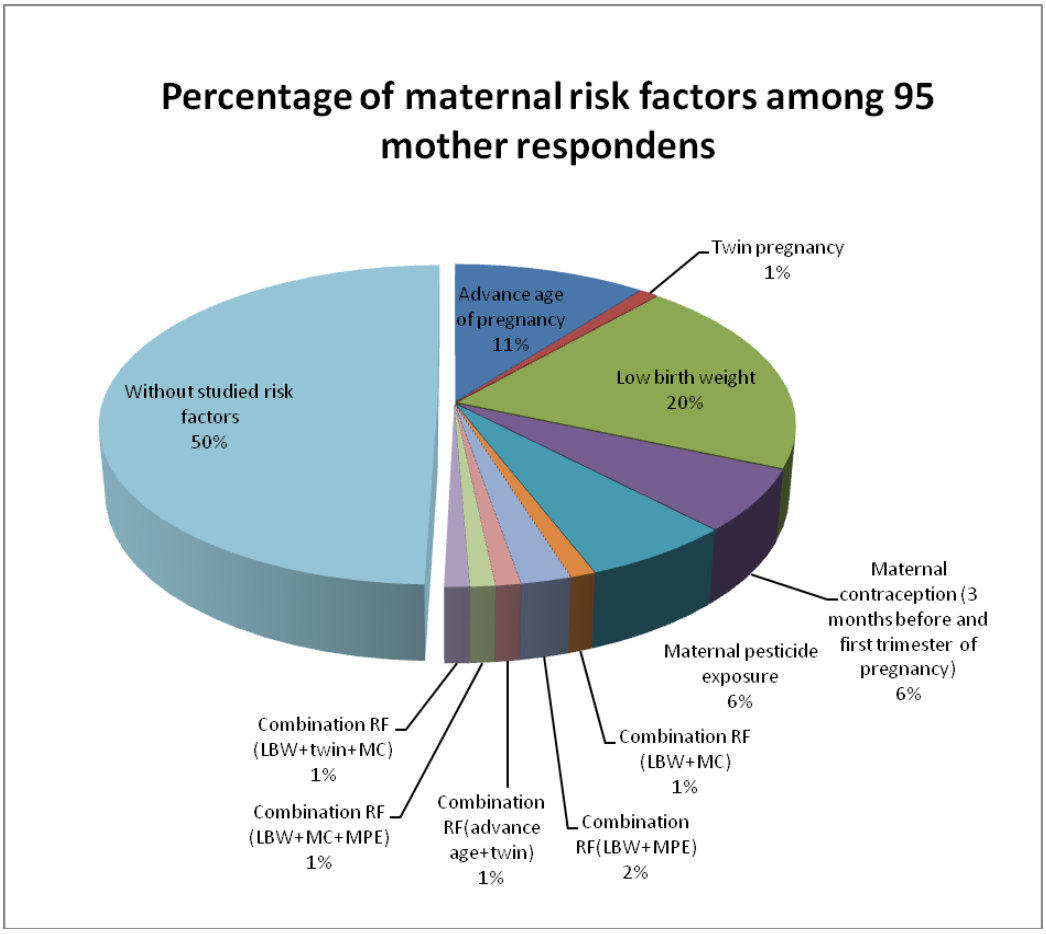


Series 1 : respondent with risk factor

Series 2 : respondent without risk factor

The percentage of each risk factor in mother including its combination is shown in pie diagram 2.2.

Diagram 2.2



RF : risk factor, LBW : low birth weight, MC : maternal contraception, MPE : maternal pesticide exposure.

The highest percentage in maternal risk factor among 95 respondents are low birth weight (20%), followed by advance age of pregnancy (11%), maternal contraception (6%), maternal pesticide exposure (6%), combination of LBW-MPE (2%), and twin pregnancy, combination of LBW-MC, combination of LBW-MC-MPE, combination of LBW-twin-MC, combination of advance age-twin have a same percentage, 1%.

DISCUSSION

Data of paternal risk factors shown that paternal active smoking is the most occurring risk factor with its proportion is 49% or 39% when it occurs as sole risk factor. A study conducted in Rotterdam shows that from 41 hypospadia patients there are 29 fathers of patients who are smoker and the OR of paternal smoking is 3.4 (95% CI). The possible explanation has been demonstrated from animal study showed that nicotine, cigarette smoke, and/or polycyclic aromatic hydrocarbons can cause testicular atrophy, poor sperm morphology, and overall impaired spermatogenesis.[10] Moreover, in smokers, the estradiol level increase and it can impair spermatogenesis through different pathways include the alteration of HPG (Hypothalamic Pituitary Gonadal) axis.[10] Nevertheless, smokers in this study does not show low level of sperm count. In tshe opposite, respondents with low level of sperm count (or sub fertile status) revealed not smoke.

Previous study mentioning that there are correlations of family cluster with hypospadia are not shown in this study.[5] Among all of the patients gathered, none of their father had hypospadia history and only one father had crytorchidism history. It is in contrast with the previous study mentioning that abnormalities of scrotum or testes like cryptorchidism were found in 34% of index fathers whose sons had hypospadia.[5] There are only 2 respondents with sub fertile status in this study. Other study found that 24% of fathers with affected sons had sign of sub fertility (low level count of sperm, decrease in sperm motility, density, and morfology).[5] However, father with cryptorchidism history in this research was found to have no subfertility

problem, and in reverse father with subfertility status has no previous cryptorchidism history.

In this research finding, there are 16 fathers (17%) with risk factors of pesticide exposure in 3 months before and during first trimester of pregnancy. The pesticides that mostly used are insecticide, fungicide, sold disinfectant, and herbicide, respectively. There is no clear mechanism how paternal pesticide exposure interfere the early development of fetus. The suggested mechanism is seminal fluid might act as potential vehicle of contaminant to the ovum or early embryo. Another simple explanation is that father may carry home chemical compound from his tools and clothes.[11]

Some respondents are found to have more than one risk factor. It might explain that hypospadia is multifactorial disease which could be happened from interaction of genetics, endocrine, and environment factor.[1,2,7]

The risk factors shown in this study are not only come from parent itself, but also from the characteristic of pregnancy like birth weight and twin pregnancy.[2]

In this research finding, the most occurring maternal risk factor is low birth weight. It is 24 respondents or 25% of respondents. Previous study found that there is a correlation between hypospadia and low birth weight which shown by 2.3 of OR (95% CI:1.2-4.2).[2] Low birth weight might be a sign that there is a growth restriction in fetus due to the insufficient of placenta to provide nutrients and gonadothropin (like Human Chorionic Gonadotropin/HCG) for fetus, since HCG plays a role in male sexual differentiation.[2] This explanation also demonstrates how twin pregnancy

correlates with hypospadia. In this research, there are 3 mothers who had twin children. There is 1 pair of monozygotic twin who had hypospadia. The monozygotic twin in this finding is male-male pair consistent with previous study where hypospadia is likely affect male-male pair than male-female pair.[5]

Advance age of pregnancy associated with severe cases of hypospadia was shown in California study. Fifty percent of severe cases was born from mother older than 35 years old in pregnancy.[12] This correlation might be due to the bioaccumulation of xenobiotics as advancing body burden of persistent, which may be interfere with both estrogen and androgen control of development.[3] In this study, it had also been found that 11 mother gave birth in age of 35 or older. The oldest age in this research finding is 46 years old. The average age of pregnancy in this study is 26.8 years old.

This research has found that there are 9 mothers who used contraceptives agent during 3 months before and first trimester of pregnancy. Other study conducted in Nijmegen indicated that oral contraceptive use after conception might be associated with hypospadia.[2] In contrast, the study in Hungaria demonstrated that there is no association between oral contraceptive use during earlier of pregnancy with the increase incidence of hypospadia in offspring.[13] In this study, the researcher had found not only oral contraceptive but also other kind of contraceptives like injection contraceptive and IUD hormonal were used. The most contraceptive used is injection contraceptive. There is only one respondent were using oral contraceptive, and one respondent were using IUD hormonal in that such of period. Those kinds of

contraceptives contain of progesterone or progesterone and estrogen. Previous study proposed that estrogen and progesterone may act as inhibitor of male genital development.[14] Progesterone itself acts as competitive inhibitor of testosterone to dehidrotestosterone conversion.[5,15]

Other endocrine disrupting chemical is pesticide. This study found 9 mothers (10%) were exposed to pesticide during that such of period, where all of them were exposed to insecticide. A study in US demonstrated that nearly 60% of herbicide used have endocrine and reproductive effect in animal (in vitro study).[16] Pesticide, such as vinclozoline, procymidone, linuron, and fenitrothrion act as androgen receptor antagonist, while phthalate esters (PE) acts as testosterone synthesis inhibitor.[5] Unfortunately, there is no additional information about the contain of pesticide in this research finding because the exact active chemical substance in pesticide is unknown by the respondents.

In this research, there are 6 mothers with more than one risk factor. There are 5 kind combinations of risk factor involving environmental factor, endocrine factor, maternal factor, and characteristic of pregnancy. It is possibly explain that multifactor aspects influence the development of hypospadia.[1,2]

The conclusion based on the result and discussion above is that the proportion of paternal risk factor with descending fashion respectively are active smoking, pesticide exposure, subfertile status, cryptorchidism history, and hypospadia history, while in mother are low birth weight, advance age of pregnancy, maternal

contraception, pesticide exposure, and twin pregnancy. Some respondents who had more than 1 risk factor might explain that hypospadia occurs as multifactorial disease.

Case control design with matching and large sample in Indonesia is needed to get a better conclusion. More studies about risk factor of hypospadia particularly in Indonesia is needed to gather more information about suggested risk factor as the etiology and still needed to seek other possible risk factors that might play a role in etiology of hypospadia.

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